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# Efficient catalytic oxidation of primary and secondary alcohols using a non-heme dinuclear iron complex

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**A novel μ-oxo diiron(III) complex is capable of fast and selective oxidation of primary and secondary alcohols in the presence of $H_2O_2$ and a remarkable increase in reaction rate is achieved by addition of 1 eq. of $CF_3SO_3H$.**

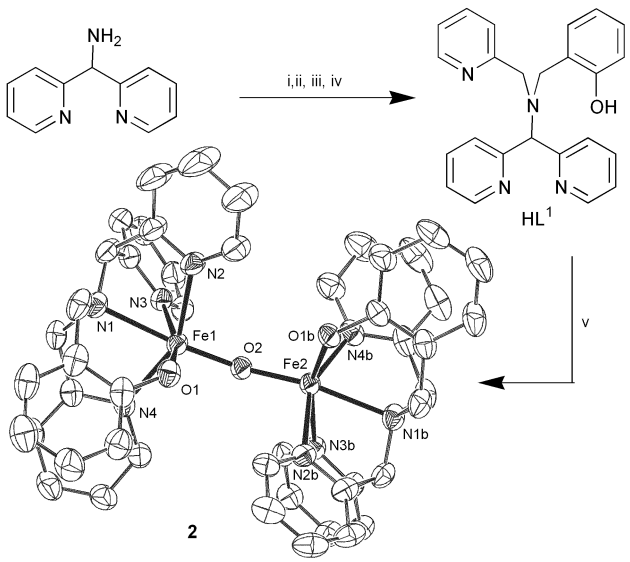
In nature, a variety of non-heme metalloenzymes are present which are capable of oxidation of substrates with high turnover frequencies and excellent selectivity.[1] An example is the mononuclear copper enzyme galactose oxidase (GOase) which catalyses the aerobic oxidation of benzylic and allylic alcohols to their corresponding aldehydes with concomitant formation of $H_2O_2$. The study of model complexes not only provides invaluable information about metalloenzymes, but also can result in the development of new generations of oxidation catalysts.[2] Beautiful examples are the GOase models developed by the groups of Wieghardt and Stack, which are capable of oxidation of alcohols to the corresponding aldehydes with high yield and selectivity.[3] An iron(II) complex of a pentadentate ligand N4Py† was developed as a model system for Fe-BLM.[4,5]† This system is capable of oxidising alkanes using $H_2O_2$ *via* a radical type mechanism. To explore the effect of ligand variations on the oxidation behaviour of the complex, we prepared a ligand $HL^1$† in which one of the pyridyl groups is replaced by a phenolate moiety. The corresponding μ-oxo dinuclear iron complex of $HL^1$ proved to be a selective and efficient catalyst for the oxidation of alcohols to aldehydes and ketones using $H_2O_2$ as the oxidant. Yields up to 65% based on $H_2O_2$ can be reached.

The synthesis of $HL^1$ is shown in Scheme 1. Complexation of the ligand with $Fe(II)(ClO_4)_2 \cdot x\,H_2O$ in MeOH, in the presence of 1 eq. of $Et_3N$ followed by slow diffusion of ethyl acetate into the methanolic solution yielded purple crystals of complex **1** ($\lambda_{max}$ = 540 nm, $\varepsilon_M$ = 5.6 $10^3$ $M^{-1}$ $cm^{-1}$) in 50% yield.‡ The complex was characterised as an antiferromagnetically coupled diiron(III) species based on its EPR silent nature and its $^1$H-NMR spectrum, which exhibits paramagnetically shifted signals in the 0–40 ppm range. The ESI/MS spectrum shows a peak at *m/z* 445 ($[(L^1)Fe(\mu\text{-}O)Fe(L^1)]^{2+}$), which is consistent with the formulation of **1** as $\{[(L^1)Fe(\mu\text{-}O)Fe(L^1)](ClO_4)_2\}$. Further proof for this assignment was obtained from the crystal structure of the corresponding μ-oxo diiron(III) complex $[(L^1)Fe(\mu\text{-}O)Fe(L^1)](PF_6)_2$ (**2**), depicted in Scheme 1, which was synthesised by adding $Fe(NO_3)_3 \cdot 9H_2O$ to a solution of the ligand in methanol, followed by the addition of 1 eq. of $Et_3N$ and 2 eq. of $NH_4PF_6$. Dark purple–blue crystals were obtained by slow diffusion of ether into the solution of **2**. Each iron(III) ion adopts a distorted octahedral coordination geometry involving a tertiary amine, three pyridine nitrogens, a phenolate oxygen atom and the bridging oxygen atom, with the Fe–O–Fe angle being 151.22(10)°.§ The crystal structure of **2** gave no indications that a proton is present at the phenolate moiety, which is consistent with the ESI/MS results of **1** (*vide supra*).

Complex **1** was examined as a catalyst (0.1 mol%) in the oxidation of various substrates using $H_2O_2$ as the oxidant.¶ Primary and secondary alcohols are oxidised rapidly (Table 1).‖

The oxidation of benzyl alcohol was monitored in time by GC. In Fig. 1 the turnovers per iron centre are plotted against time. Surprisingly, already 4 eq. of benzaldehyde have been formed in a reproducible manner, 30 s after the reaction was started by adding $H_2O_2$. The origin of this initial burst of activity is unclear. After the initial oxidation, a lag phase was observed. A significant increase in catalytic activity occurred after approximately 40 min and after 75 min the catalytic activity ceased because all the $H_2O_2$ was consumed. A total of 50 turnovers towards benzaldehyde was reached. Although a trace of benzoic acid was obtained, no other side products were produced according to GC. When another aliquot of $H_2O_2$ is added after 90 min, the catalyst is immediately active and no lag phase is observed. A value of 96 turnovers per iron centre can be obtained after 180 min. This can be repeated at least 3 times without significant loss of activity, showing a good stability of the system during catalytic turnover.

The UV/Vis absorption of **1** at 540 nm was monitored concomitantly with the oxidation of benzyl alcohol to benzaldehyde. During the lag phase the solution remains purple but after 45 min the colour changes to yellow. This colour change coincides with the end of the lag phase, suggesting that the yellow species is responsible for the oxidation activity.




**Scheme 1** Synthesis of $HL^1$ and **2** and crystal structure of the cation of **2** (displacement ellipsoid plot with 50% probability level in which hydrogen atoms are omitted for clarity). *Reagents and conditions*: i, 2-pyridine carbaldehyde, 2 h, 97%; ii, $NaBH_4$, MeOH, 2 h, 90%; iii, 2-(bromomethyl)phenyl acetate, $^iPr_2EtN$, EtOAc, 3 d, 66%; iv, $K_2CO_3$, MeOH, 1 h, 89%; v, $Fe(NO_3)_3$, $Et_3N$, $NH_4PF_6$, 29%; Selected interatomic distances (Å): Fe–O: 1.93, Fe(1)–O(2) 1.79, Fe(1)–N(1) 2.26, Fe(1)–N(2) 2.17Å, Fe(1)–N(3) 2.22, Fe(1)–N(4) 2.13.

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**Table 1** Turnover numbers (t.o.n.) of the catalytic oxidation experiments with **1** using $H_2O_2$

| Entry | Substrate | Product | Time/min | t.o.n.[a] |
|---|---|---|---|---|
| 1[b] | Benzyl alcohol | Benzaldehyde | 75 | 50 |
| 2[c] | Benzyl alcohol | Benzaldehyde | 15 | 50 |
| 3[d] | Benzyl alcohol | Benzaldehyde | 90 | 15 |
| 4[e] | Benzyl alcohol | Benzaldehyde | 180 | 96 |
| 5 | Cyclohexanol | Cyclohexanone | 60 | 28 |
| 6 | Cyclohexanol | Cyclohexanone | 60 | 65 |
| 7 | Cyclooctanol | Cyclooxtanone | 180 | 11 |
| 8 | Octan-1-ol | Octanal[f] | 180 | 11 |
| 9 | *sec*-Phenylethyl Alcohol | Acetophenone | 60 | 50 |

[a] t.o.n. = mol product/mol catalyst. [b] In the absence of catalyst a negligible amount of 0.004 mmol of benzaldehyde was formed under the standard reaction conditions after 90 min, whereas in the presence of $Fe(II)(ClO_4)_2$ only 8 turnovers were reached. [c] In the presence of 1 eq. $CF_3SO_3H$. [d] With 100 eq. of substrate instead of 1000 eq. [e] Addition of another aliquot of $H_2O_2$ after 90 min. [f] Octanoic acid was formed as side product.

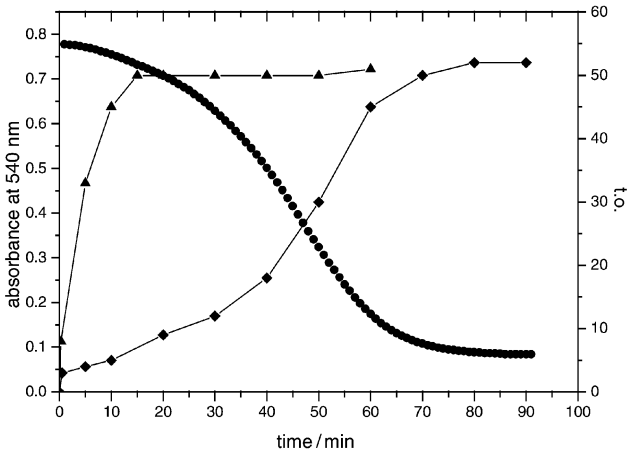


**Fig. 1** Catalytic oxidation of benzyl alcohol to benzaldehyde using **1**: (■) time course of the turnovers, (●) time dependent decay of the UV band at $\lambda$ = 540 nm and (▲) oxidation in the presence of 1 eq. $CF_3SO_3H$.

Several observations suggest that the active oxidising complex is a mononuclear species. First, complex **1** is EPR silent whereas upon addition of benzyl alcohol and $H_2O_2$, when the solution becomes yellow, a strong EPR signal can be observed at $g$ = 4.3 which is characteristic for a mononuclear high-spin iron(III) complex.[6] Secondly, it was found that alcohols, which are known to be capable of breaking up the oxo-bridge of some dinuclear iron μ-oxo complexes to form monomeric structures by coordination to the metal centre,[6] are oxidised rapidly. In contrast, the active yellow species is formed very slowly in the absence of substrate or with a non-coordinating substrate like cyclohexene. Finally, we envisaged that protonation of the oxo-bridge in **1** would facilitate the formation of the mononuclear species and hence would speed up the reaction. Upon addition of triflic acid ($CF_3SO_3H$) to **1** in acetone a blue colour appears. The $^1$H-NMR spectrum of this solution shows broad signals in the −10 to 120 ppm range consistent with the presence of mononuclear high-spin Fe(III) species. The ESI/MS spectrum shows prominent peaks at $m/z$ 581 and 472, which corresponds to $[L^1Fe^{III}\text{-}OTf]^+$ and $[(HL^1)Fe^{III}(OH)_2]^+$, respectively. Indeed when $CF_3SO_3H$ (1 eq.) was used, the reaction rate increased dramatically (Fig. 1). The yellow species was formed immediately upon addition of $H_2O_2$ and after 15 min already 50 turnovers are reached in the oxidation of benzyl alcohol.

Although the exact reaction mechanism is not known yet, some tentative conclusions can be drawn. The fact that benzene, which can act as a hydroxyl radical trap,[5] is not oxidised by this system, combined with the large kinetic deuterium isotope effect (KIE, $k_H/k_D$ = 4.0) that was observed in a competition experiment between benzyl alcohol and benzyl alcohol-$d_7$, it can be concluded that oxidising species more selective than hydroxyl radicals are present. When the KIE was determined 30 s after starting the reaction by addition of $H_2O_2$, *i.e.* after the initial burst of activity, a value of 1.8 was obtained indicating the presence of a highly reactive oxidising species in the initial stage of the reaction. Finally, since the purple colour of **1** is indicative of a LMCT transition between the phenolic part of the ligand and the iron(III) center,[7,8] it is most likely that the phenolic moiety is no longer coordinated to the iron centre in this yellow species, which is thought to be responsible for oxidation activity.

In conclusion, a new Fe(III) containing catalyst has been developed for selective oxidation of primary and secondary alcohols using $H_2O_2$. A dramatic enhancement in the reaction rate upon addition of acid has been observed, which is attributed to accelerated formation of the active mononuclear catalyst.

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## Notes and references

† Abbreviations used: N4Py = *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine; $HL^1$ = 2-({[di(2-pyridyl)methyl](2-pyridylmethyl)-amino}methyl)phenol; Fe-BLM = iron bleomycin.

‡ Anal. calcd. for $C_{48}H_{42}N_8O_{11}Fe_2Cl_2{\cdot}H_2O$: C 52.07, H 4.01, N 10.13%; found: C 52.17, H 3.80, N 10.03%.

§ *Crystal data*: $[C_{48}H_{42}Fe_2N_8O_3](PF_6)_2$, *F*w = 1180.54, dark blue needle, 0.45 × 0.24 × 0.15 mm$^3$, monoclinic, *C*2/*c* (No. 15), $a$ = 31.0660(6), $b$ = 11.1832(2), $c$ = 33.8507(7) Å, $\beta$ = 100.6240(7)°, $V$ = 11558.7(4) Å$^3$, $Z$ = 8, $\rho$ = 1.357 g cm$^{-3}$. 83260 reflections were measured on a Nonius KappaCCD diffractometer with rotating anode ($\lambda$ = 0.71073 Å) at a temperature of 150(2) K. 10198 reflections were unique ($R_{int}$ = 0.043). *R*-values [$I > 2\sigma(I)$]: *R*1 = 0.0416, *wR*2 = 0.1173. Molecular illustration, structure checking and calculations were performed with the PLATON package. CCDC 154063. See http://www.rsc.org/suppdata/cc/b0/b009368h/ for crystallographic files in .cif format.

¶ Oxidation reactions were performed in acetone, under an argon atmosphere in a water bath thermostatted at 25 °C. In a typical reaction, 3.5 mmol of substrate (1000 eq.) was added to 4 ml of a stock solution of 1.75 μmol of the catalyst (*i.e.* 3.5 μmol of iron) and a known amount of the internal standard bromobenzene. The reaction was initiated by addition of 35 μl of $H_2O_2$ (30% solution in water, 100 eq.) and monitored by GC.

‖ Alkenes and alkanes were also investigated, but these reactions are slow (6–18 h), less selective and turnover numbers are lower (typically 10–20).

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